PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Group: 180
Garth J.S. Cooper	:	Art Unit: 186
Serial No.: 07/236,985	:	Examiner: Lester L. Lee
Filed: August 26, 1988	:	
For: TREATMENT OF DIABETES MELLITUS	:	

RESPONSE

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

In response to the Official Action dated July 19, 1989, we submit the following remarks:

1. Restriction Requirement.

Group I is provisionally elected with traverse. We submit that the restriction requirement should be withdrawn for the reasons discussed below.

The Examiner requires restriction of the original claims 1-45 into six groups:

Group I: Claims 1, 5, [9], 19, 22 and 32-33, drawn to amylin or CGRP or derivatives thereof, classified in Class 530, subclass 307. (Note: Claim 9 is listed by the Examiner in both Groups I and III; we presume it was meant to be placed in Group III.)

Group II: Claims 2-4, 6 and 23, drawn to composition of insulin and amylin or CGRP, classified in Class 514, subclass 4.

Group III: Claims 7-10, drawn to a method of treating diabetes mellitus, classified in Class 514, subclass 3.

Group IV: Claims 11-18 and 20-21, drawn to preparations of amylin and derivatives of amylin, classified in Class 514, subclass 3.

Group V: Claims 29-31 and 34-45, drawn to a method of preparation of amylin or amylin derivatives in crystalline form, classified in Class 514, subclass 3.

Group VI: Claims 36-40, drawn to a method for monitoring the therapy of diabetes or hypoglycemia, classified in Class 436, subclass 501.

Group VII: Claims 43-47 [sic, 45], drawn to a method of preparing amylin or derivatives thereof, classified in Class 530, subclass 307. (Note: Typographical error - "47" should be "45").

Claims 24-28, 41-41 [sic, 42] link inventions I and II. (Note: Typographical error - "41" should be "42").

As the Examiner is aware, §803 of the MPEP states that there are two criteria for a proper restriction requirement:

(1) The inventions must be independent or distinct as claimed, and

(2) There must be a serious burden on the Examiner if restriction is not required.

a. Independent or Distinct Inventions

(i) Groups I and III

The Examiner states that inventions I and III are related as product and process of use and that they constitute distinct inventions.

The Examiner's Group I includes:

(1) amylin, amylin-amide, CGRP, functional fragments thereof, and conservative variants thereof (Claim 1);

(2) a method of preparing a product for the treatment of diabetes mellitus or hypoglycemia which comprises bringing amylin, amylin-amide, CGRP, functional fragments thereof, or conservative variants thereof, into the form of a solution suitable for parenteral administration (Claim 5);

(3) a preparation of one or more of amylin, amylin-amide and active subfragments thereof, that is lyophilized (Claim 19);

(4) a delayed release preparation of one or more of amylin, amylin-amide, and active subfragments thereof (Claim 22);

(5) a suspension of one or more of amylin, amylin-amide and active subfragments thereof formulated in a zinc buffer suitable for parenteral administration (Claim 32); and

(6) the suspension of Claim 32 wherein the zinc salt is zinc chloride (Claim 33).

The Examiner's Group III includes methods for treating diabetes mellitus or hypoglycemia (claims 7-10).

As noted by the Examiner, the test for determining whether a product and a process for using the product can be shown to be distinct inventions is whether: (1) the process can

be practiced with another materially different product, or (2) the product can be used in a materially different process. See MPEP §806.05(h).

The burden is on the PTO to provide an example. Id. The Examiner provided no example in which the process of Claims 7-10 (Group III) can be practiced with a product materially different from the products of Claims 1, 5, 19, 22, 32 and 33 (Group I).

The Examiner did, however, state that the products of Group I can be used in a process of treating hypotension. We cannot confirm that amylin will be effective in treating low blood pressure. We are aware of no studies showing that amylin or derivatives thereof are useful in treating hypotension. In addition, we are aware of no findings that CGRP is useful in treating hypotension. CGRP, in fact, is a potent vasodilator and, therefore, can cause hypotension. Moreover, we note that the characterization of amylin is a recent discovery. See Cooper et al., "Purification and characterization of a peptide from the amyloid-rich pancreases of Type 2 diabetic patients." Proc. Natl. Acad. Sci. USA; 84:8628-8632 (1987). Thus, it is unlikely that investigators in other areas, let alone those in diabetes research, will have examined the effects of amylin or its derivatives.

Accordingly, the Examiner's assertion that amylin or other claimed products can be used in a materially different process other than the claimed processes appears de minimis. Therefore, no restriction between Groups I and III should be required and we respectfully request that the Examiner withdraw this requirement.

(ii) Groups I and II

The Examiner states that inventions I and II are related as combination and subcombination and that these inventions are distinct. The test for determining whether a combination and subcombination are distinct is whether both of the following requirements are met: (1) the combination as claimed does not require the particulars of the subcombination as claimed for patentability; and (2) the subcombination has utility by itself or in other and different relations. MPEP §806.05(c)

The Examiner contends that inventions I and II constitute distinct inventions because the combination as claimed (namely, the products and methods listed in Group II, including compositions of insulin and one or more of amylin, amylin-amide, CGRP, functional fragments thereof, or conservative variants thereof) do not require the particulars of the subcombination as claimed for patentability (namely, the products and methods of Group I) because the compositions of Group II can be used to "monitor the treatment of hypoglycemia" and that the Group I subcombination "has separate utility such as in the treatment of hypotension."

The significance of the Examiner's statement that the combinations of Group II can be used to monitor the treatment of hypoglycemia is unclear. Applying the test set forth in the MPEP, the pertinent question would appear to be whether the combinations of Group II (insulin plus one or more of amylin, amylin-amide, CGRP, functional fragments thereof, or conservative variants thereof) require certain particulars of Group I (amylin, amylin-amide, CGRP, functional fragments thereof, or conservative variants thereof) for patentability.

This question is answered in the affirmative, as insulin alone is an old product and, thus, not patentable. The invention described in this application is based on the discovery that the Type 1 diabetic syndrome results from a deficiency of not one hormone (insulin, as previously thought), but two (insulin and amylin). While the claims of Group I and II plainly stand alone in terms of patentability, i.e., they do not stand or fall together, the claims share important features and should be examined together.

Additionally, we believe the Examiner's concern that the subcombination has separate utility in the treatment of hypotension to be inapplicable, for reasons noted above.

Because neither of the two criteria for restriction of subcombination and combination inventions is satisfactorily met, we respectfully request that the Examiner withdraw the restriction requirement with respect to Groups I and II.

(iii) Groups I and IV

The Examiner contends that inventions I and IV are related as mutually exclusive species in intermediate-final product relationship. The Examiner correctly states the rule applied to intermediate-final product relationships, i.e., distinctness is shown only if the intermediate product is useful other than to make the final product. MPEP §806.04(b)

However, the relationship between Group I and Group IV is not that of mutually exclusive species in intermediate-final product relationship. The claims of Group IV relate to the preparations of amylin, amylin-amide, and active subfragments thereof which have been rendered soluble. The contents of

Group I include Claim 1 which pertains to amylin, amylin-amide, CGRP, functional fragments thereof, or conservative variants thereof, for the treatment of diabetes mellitus or hypoglycemia; and Claim 5, which describes a method of preparing amylin, amylin-amide, CGRP, functional peptide active subfragments thereof, and conservative variants thereof, into the form of a solution.

Claims 12-18 of Group IV relate to methods of preparation, the claims of Group I to certain products. Further, no showing has been made that the products of these methods can be used other than to make amylin products, such as those of the Group I claims. With respect to Claim 5, the Examiner appears to be arguing that a method and preparations can be related as intermediate-final product. Products may be intermediates, but methods may not.

The remaining claims of the Examiner's Group I, Claims 19, 22, 32 and 33, pertain to lyophilized preparations, delayed release preparations and suspensions. The Examiner's reasoning as to why lyophilized preparations, delayed release preparations and suspensions are intermediates in the process of making soluble preparations is unclear. Even if the Groups I and IV contain claims to intermediate and final products, respectively, the test set forth in the MPEP is not satisfied. Applicant respectfully suggests that this requirement for restriction is inappropriate.

(iv) Groups I and V

The Examiner makes the same intermediate-final product argument with respect to Groups I and V. Group V contains claims

to certain preparations in which differing durations of action are provided by certain procedures involving crystallization.

Groups I and V are not related as intermediate-final product unless one requires that the "final" product be in crystalline, delayed action form. Therefore, the Examiner's argument appears to be inapplicable here.

The Examiner's contention that the intermediate product is deemed to be useful as a method of treating diabetes mellitus illustrates that the claims of Group I and the claims of Group V, rather than identifying intermediate and final products, "are but different definitions of the same subject matter, varying in breadth or scope of definition." MPEP §806.03. The claims of Group V define a narrower group of preparations, that is, those preparations containing crystallized amylin, crystallized amylin-amide and active subfragments thereof. Therefore, restriction should not be required. Id.

(v) Groups I and VI

The Examiner states that inventions I and VI are related as product and process of use. Group VI includes claims to a method of monitoring the therapy of diabetes or hypoglycemia comprising determination of the level of circulating amylin in a patient undergoing said therapy. The asserted relationship to the claims of Group I is not understood and, as such, is submitted to be in error. The Group VI claims relate to a process of monitoring the effects of administration of the Group I products, not to a process of their use.

The Examiner's argument that the compounds of Group I have utility in the treatment of hypotension is responded to above.

(vi) Groups I and VII

The Examiner states that inventions I and VII are related as process of making and product made. Group VII contains claims which describe methods for denaturing and oxidizing amylin, amylin-amide or subfragments thereof.

This characterization of the relationship between the claims in Group I and the claims in Group VII as product/process is only in part accurate. The methods claimed in Group VII, pertaining to denaturing and oxidizing amylin, amylin-amide and subfragments thereof, are methods that relate to formation of a Cys^2-Cys^7 disulfide, needed for complete biologic activity of amylin and CGRP.

b. Serious Burden on the Examiner

The Examiner states that the inventions of Groups I-VII are distinct and "have acquired a separate status in the art as shown by their different classification[s]" and "because of their recognized divergent subject matter." The Examiner also states that "the search for Group I is not required for Groups II-VII."

First, the claims of the application, which the Examiner has organized into Groups I-VII, do not pertain to divergent subject matter. All 45 claims of the application pertain to compounds and methods for the treatment of diabetes based on the effects of compounds having amylin-like activities.

Secondly, the characterization of amylin, a hormone isolated from the pancreatic amyloid masses typically found in Type 2 diabetic subjects, which is structurally similar to calcitonin gene related peptide (CGRP), and the discovery of amylin's biological effects are recognized to constitute applicant's pioneering work. Additionally, the discovery that

amylin is co-secreted with insulin, and that replacement of amylin with insulin as described and claimed herein will be of benefit to diabetics, is a new and fundamental discovery.

Furthermore, the Examiner's assertion that the search for Group I is not required for Groups II-VII appears incorrect. Group I includes: (1) amylin, amylin-amide, CGRP, functional fragments thereof, and conservative variants thereof (Claim 1); (2) a method of preparing a product for the treatment of diabetes mellitus or hypoglycemia which comprises bringing amylin, amylin-amide, CGRP, functional fragments thereof, or conservative variants thereof, into the form of a solution suitable for parenteral administration (Claim 5); (3) a preparation of one or more of amylin, amylin-amide and active subfragments thereof, that is lyophilized (Claim 19); (4) A delayed release preparation of one or more of amylin, amylin-amide, and active subfragments thereof (Claim 22); (5) a suspension of one or more of amylin, amylin-amide and active subfragments thereof formulated in a zinc buffer suitable for parenteral administration (Claim 32); and (6) the suspension of Claim 32 wherein the zinc salt is zinc chloride.

The search for prior art relevant to the listed preparations and methods seems exactly the search which would be appropriate for the claims of Groups II-VII as well. Because the characterization of amylin and the discovery of its biological effects are so recent, there will be little, if any, prior art for the Examiner to search with respect to <u>any</u> of the Groups. Thus, searching prior art with respect to all claims will create no serious burden on the Examiner. Therefore, we respectfully submit that the Examiner's requirement of restriction of the

invention to one of the Examiner's Groups I-VII is improper under MPEP §803.

c. Alternative Groups

In the event the Examiner nevertheless requires restriction of the original claims, we respectfully suggest that the following groups would be more appropriate:

Group A: Claims 1-10, drawn to a method of treating diabetes mellitus or hypoglycemia comprising the administration of amylin, amylin-amide, CGRP, a functional peptide fragment thereof, or a conservative variant thereof, with or without the concomitant administration of insulin, along with the products and compositions involved and methods for preparing such products and compositions;

Group B: Claims 11-21, drawn to soluble preparations of amylin, amylin-amide or subfragments thereof;

Group C: Claims 22-35, drawn to delayed release preparations of amylin, amylin-amide or subfragments thereof;

Group D: Claims 36-40, drawn to a method for monitoring the therapy of diabetes mellitus or hypoglycemia; and

Group E: Claims 43-47 [sic, 45], drawn to a method for preparing amylin, amylin-amide, or subfragments thereof, comprising denaturation and oxidation

Linking Claims: Claims 41-42 link Groups B and C

Groups B, C and E should be examined together. On review of the claims in Groups B, C and E, the Examiner will note that the claims in Groups B, C and E relate to modifications in the basic products, compositions and methods of Group A. For example, the soluble preparations of Group B enable the products and compounds claimed to enter into the circulation, the delayed release preparations of Group C are desirable for therapeutic efficacy, and the denaturation and oxidation methods of Group E affect the biological activity of the claimed products and compounds. Accordingly, it would be efficient to examine Groups B, C and E together.

No additional searching burden is placed on the Examiner because the characterization of amylin and the recognition of its (and hence CGRP's) effects is so new that there is little, if any, prior art to be considered.

d. Conclusion on Restriction Requirement

We respectfully request that the Examiner withdraw the restriction requirement for the reasons stated above.

In the alternative, we respectfully suggest that the Examiner organize the claims into new Groups A, B, C, D and E and examine Groups B, C and E together.

If the Examiner chooses to modify the restriction requirement to incorporate the new Groups A, B, C, D and E, but determines to examine them each separately, we elect new Group A.

2. Requirement For Election Among Species.

The Examiner requires election of "a single disclosed species of amylin or CGRP derivative," and lists the following

such species: (1) amylin; (2) amylin-amide; (3) CGRP; (4) specific peptide fragment of amylin or CGRP; or (5) specific conservative variant of amylin or CGRP.

In response to the Examiner's requirement for election among species, applicant provisionally elects "amylin-amide." Applicant has determined, however, that "amylin-amide" is the naturally-occurring molecule, i.e., that "amylin" is amidated in its natural state. Thus, it is appropriate to here elect "amylin." Deamidated amylin also falls within the scope of the invention and, henceforth, these species will be so-identified rather than as "amylin" and "amylin-amide." All claims read on the provisionally elected species. The requirement for election among the species is respectfully traversed.

The policy behind the election of species requirement is to avoid waste of the Examiner's time to search the subject matter of several species claims in the event that the generic claim encompassing such species claims is ultimately determined to be unpatentable. See MPEP §809.02(c)(2)(i) ("When a generic claim is subsequently held to be allowable ... and all claims are embraced by an allowable generic claim ... applicant should be advised of the allowable generic claim and that the claims to the non-elected species are no longer withdrawn since they are fully embraced by the allowed generic claim" (emphasis added).

In this instance, because the subject matter of all claims of the application is so new, there will be little, if any, prior art for the Examiner to search with respect to any of the claims. Therefore, the policy behind the election of species requirement is inapplicable and restriction of species should not be required in this case.